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PATENT ABSTRACTS OF JAPAN

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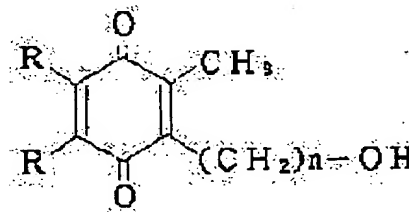
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(54) PREVENTIVE AND THERAPEUTIC AGENT FOR DIABETIC COMPLICATION

(57)Abstract:

PURPOSE: To obtain a safe preventive and therapeutic agent useful for diabetic complications such as nephritis, retinitis, neuropathy, arteriosclerosis, thrombosis, cataract, iritis and gangrene caused by superoxide dismutase produced from saccharified proteins in the body of a patient suffering from diabetes.

CONSTITUTION: A safe preventive and therapeutic agent for diabetic complications, containing a compound expressed by the formula [R is methyl or methoxy or two groups R are bonded to form one butadienylene; (n) is an integer of 4-22, preferably 7-15, especially 9-13] or its hydroquinone derivative, e.g. idebenone [2, 3-dimethoxy-5-methyl-6-(10-hydroxydecyl)-1,4-benzoquinone] as an active ingredient and having low toxicity. The aforementioned compound can orally or parenterally be administered in various dosage forms such as a tablet, a granule, a capsule, an injection or a suppository to patients suffering from diabetes. The normal dose of the aforementioned agent for an adult is 0.1-500mg, preferably 5-200mg per day in the case of oral administration.



LEGAL STATUS

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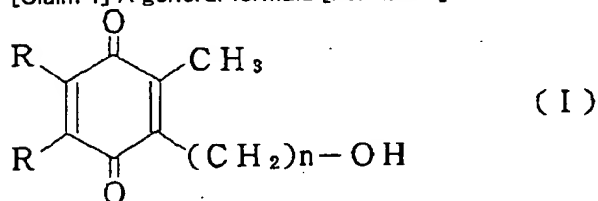
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CLAIMS

[Claim(s)]

[Claim 1] A general formula [Formula 1]



[— among a formula, respectively a methyl group or a methoxy group is shown, or two R joins together, R shows the butadienylene group of a piece, and, as for n, the integer of 4-22 is shown.] the diabetic inside of the body which comes out and makes an active principle the compound expressed or its hydroquinone object — saccharification — prevention / therapy agent of the diabetic complication resulting from the super oxide produced from protein.

[Translation done.]

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DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Industrial Application] This invention relates to prevention / therapy agent of diabetic complication.

[0002]

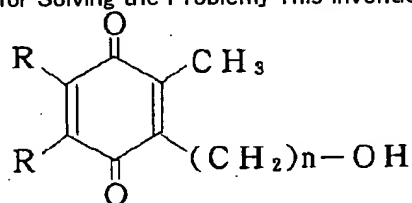
[Description of the Prior Art] Generally, by the diabetic, saccharification of the nonenzymatic protein by hyperglycemia is accelerating and, on the other hand, various diabetic complication, such as arteriosclerosis, a nephropathy, and a retinopathy, is caused. Such complication is considered in a possibility of originating in the vascular endothelial cell failure by super oxide. however, saccharification — the relation between that there is much protein and generation of super oxide is not solved.

[0003]

[Problem(s) to be Solved by the Invention] the result to which this invention persons took lessons from the super oxide production device and the super oxide production inhibitor, and inquired wholeheartedly from such a viewpoint — saccharification — that super oxide generates by the autoxidation of protein, the 1, 4-benzoquinone which are expressed with a general formula (I), and the hydroquinone object of those found out having super oxide production depressant action, and completed this invention.

[0004]

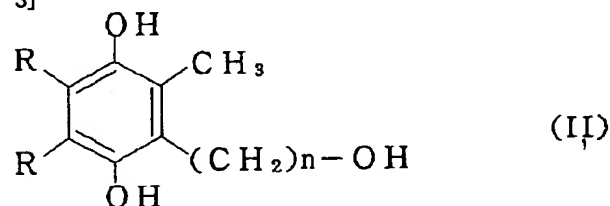
[Means for Solving the Problem] This invention is a general formula. [Formula 2]



[— among a formula, respectively a methyl group or a methoxy group is shown, or two R joins together, R shows the butadienylene group of a piece, and, as for n, the integer of 4–22 is shown.] the diabetic inside of the body which comes out and makes an active principle the compound expressed or its hydroquinone object — saccharification — it is related with prevention / therapy agent of the diabetic complication resulting from the super oxide produced from protein.

[0005] 7–15 are desirable the inside n of the compound expressed with said general formula (I), and 9–13 are more desirable. As an example of representation of a compound expressed with a general formula (I), IDEBENON [2 and the 3-dimethoxy-5-methyl-6-(10-hydroxy DESHIRU)-1, 4-benzoquinone] is mentioned.

[0006] The hydroquinone object of a compound expressed with said general formula (I) is a general formula. [Formula 3]



(— each mark is the above and this meaning among a formula.) — it is the compound expressed. In addition, since the interconversion of the compound expressed with a general formula (I) and its hydroquinone object (II) can be carried out under physiological conditions, these compounds of each other are considered as an equivalence compound in pharmacology. Generally, the direction of a quinone compound (I) tends to deal with a hydroquinone object (II) in order to tend to oxidize chemically.

[0007] if it hits using as a prevention / therapy agent of diabetic complication which described above the compound expressed with said general formula (I) — the very thing — according to a well-known method, it is various pharmaceutical forms, such as a tablet, a granule, a capsule, injections, and a suppository, and a diabetic can be medicated taking-orally-wise or parenterally. Although a dose is different with the class of object disease, a

symptom, etc., generally in internal use, 0.1mg - 500mg per day is 5mg - 200mg preferably in an adult.
 [0008] saccharification [in / in prevention / therapy agent of the diabetic complication of this invention / a diabetic] — it is used for prevention and therapies, such as the nephropathy resulting from the super oxide produced from protein, a retinopathy, neuropathy, arteriosclerosis, thrombosis, a cataract, iritis, and a gangrene.
 [0009]

[Example] The following examples of an experiment and examples explain an operation and embodiment of this invention concretely.

an example of experiment 1 purification Homo sapiens fibrinogen — a glucose — ****(ing) — saccharification — the fibrinogen was produced. IDEBENON was added to this, and in order to see the amount of generation of super oxide, the wavelength of 550nm, 37 degrees C, and the absorbance change for 10 minutes were measured by the cytochrome C method. As contrast, the same test was performed only using the nonsugar-ized fibrinogen without using IDEBENON. A result is as given in [a table 1].

[A table 1]

	スーパーオキサイド量 (550nmに於ける吸光度変化)	
	10分後	20分後
非糖化フィブリンゲン (300mg/dℓ)	0.0062 ±0.0033	0.0070 ±0.0042
糖化フィブリンゲン (フィブリ ノーゲンとして300mg/dℓ)	0.0135 ±0.0041	0.0186 ±0.0040
糖化フィブリンゲン +イデベノン(300ng/mg/ℓ)	0.0010 ±0.0010	0.0020 ±0.0012

a nonsugar-ized fibrinogen — comparing — saccharification — in the fibrinogen, there was much generation of super oxide and generation of super oxide was controlled by addition of IDEBENON.

[0010] The CE-2 powder feed (made in Japanese Clare) which contains 0.05% of IDEBENON in the femininity KKAY mouse 1 of 24 weeks old of examples of an experiment was given for four weeks, it collected urine for 24 hours, and the amount of albumin excreted into urine was calculated. A result is as given in [a table 2].

[A table 2]

被検 化合物	投与量 mg/kg/日	体重 g	血漿 血糖 mg/dℓ	尿 中 排 泄 量		
				総蛋白 (P) mg/ℓ	アルブミン(A) mg/ℓ	A/P (%)
対照群	0	39.2 ±2.3	380 ±81	47.6 ±13.9	9.61 ±3.00	20.3 ±4.1
イデベノン	90 ±14	39.5 ±2.1	397 ±69	45.3 ±12.7	6.57* ±3.71	13.9** ±3.5

Mean±SD. (例数:12匹) *P<0.05. **P<0.01
 投与量は摂取量から求めた。

- 1) K K A マウスは4週齢後、高血糖・尿糖陽性などの重篤な糖尿病状態の発現に加えて、糖尿病性腎症を発症し[ブレイン ベッセルズ(Brain vessels)、24巻、297頁(1987)]、顕著なアルブミン尿を示す。

The sample compound decreased the amount of albumin elimination in urine / total protein ratio, without influencing the onset and weight increase of hyperglycemia in a KKAY mouse.

[0011] Example 1 (1) IDEBENON of pharmaceutical preparation 20 g (2) lactose 198g (3) amyllum maydis 40g (4) magnesium stearate Paste made from 2g (1), (2), and 15g amyllum maydis It granulated, 10g amyllum maydis and (4) were added to this, mixture was compressed with the compressed tablet machine, and 1000 tablets with a diameter of 5mm which contains (1)20mg per tablet 1 lock were manufactured.

[0012]

[Effect of the Invention] saccharification [in / toxicity is low, is safe for prevention / therapy agent of the diabetic complication which comes to contain the compound expressed with the general formula (I) used in this invention or

its hydroquinone object and / a diabetic] — it is useful to diabetic complication, such as the nephropathy resulting from the super oxide produced from protein, a retinopathy, neuropathy, arteriosclerosis, thrombosis, a cataract, iritis, and a gangrene.

[Translation done.]